CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074836

Trade Name : ACYCLOVIR TABLETS 400MG AND 800MG

Generic Name: Acyclovir Tablets 400mg and 800mg

Sponsor : Zenith Goldline Pharmaceuticals, Inc.

Approval Date: April 22, 1997

74836

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074836

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074836

APPROVAL LETTER

ANDA 74-836

APR 22

Zenith Goldline Pharmaceuticals, Inc.
Attention: Karen Rocco
140 Legrand Avenue
Northvale, NJ 07647

Dear Madam:

This is in reference to your abbreviated new drug application dated January 9, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your amendment dated March 26, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Tablets, 400 mg and 800 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Tablets, 400 mg and 800 mg, respectively, of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

4/22/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074836

FINAL PRINTED LABELING

Zenith Goldline

NDC 0172-**4267**-60

ACYCLOVIR

TABLETS

400 mg

100 TABLETS (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
PROTECT FROM MOISTURE
NDC 0172-4267-60
Each Tablet Contains:
Acyclovir 400 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0197K

N 3 0172-4267-60 2

LOT:

EXP:

Zenith Goldline

NDC 0172-**4267**-70

ACYCLOVIR

TABLETS

400 mg

500 TABLETS (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
PROTECT FROM MOISTURE
NDC 0172-4267-70
Each Tablet Contains:
Acyclovir 400 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0197K

N 3 0172-4267-70 1

LOT:

EXP:

Zenith Goldline

NDC 0172-**4267**-80

ACYCLOVIR

TABLETS

400 mg

1000 TABLETS (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
PROTECT FROM MOISTURE
NDC 0172-4267-80
Each Tablet Contains:
Acyclovir 400 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0197K

N 3 0172-4267-80 0

LOT:

EXP:

Zenith Goldline

NDC 0172-4268-60

ACYCLOVIR
TABLETS

800 mg

100 TABLETS (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
PROTECT FROM MOISTURE
NDC 0172-4268-60
Each Tablet Contains:
Acyclovir 800 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0197K

N 3 0172-4268-60 9

LOT:

EXP:

Zenith Goldline

NDC 0172-4268-70

ACYCLOVIR
TABLETS

800 mg

500 TABLETS (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
PROTECT FROM MOISTURE
NDC 0172-4268-70
Each Tablet Contains:
Acyclovir 800 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0197K

N 3 0172-4268-70 8

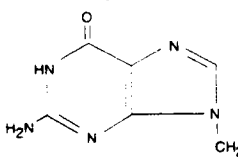
LOT:

EXP:

ACYCLOVIR TABLETS

DESCRIPTION

Acyclovir is an antiviral drug available as tablets for oral administration. It is chemically designated as 9-[(2-Hydroxyethoxy)methyl]guanine and has the following structural formula:



$C_8H_{11}N_5O_3$

M.W. 225.21

Acyclovir is a white to off-white crystalline powder with a maximum solubility in water of 2.5 mg/mL at 37°C.

Each tablet, for oral administration, contains 400 mg or 800 mg of acyclovir. In addition, each tablet contains the following inactive ingredients: corn starch, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular a-DNA polymerase, but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular a-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular a-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology

The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[7] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9-13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1,9]

Using a dye-uptake method in Vero cells,[8] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤ 0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-16] Strains with alterations in viral TK[16] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics

The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m², in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range: 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400 and 800 mg dosage regimens, respectively.

In another study, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (9.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy)methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see **DOSAGE AND ADMINISTRATION**).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE

Acyclovir tablets are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir tablets are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus orally administered acyclovir is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes *(primary and nonprimary infections-commonly known as initial genital herpes)*

Double-blind, placebo-controlled studies[23,24,25] have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes

Double-blind, placebo-controlled studies[14,26-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received acyclovir 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies[31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections

In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33] In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia).[34]

Chickenpox

In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented **within 24 hours** of the onset of a typical chickenpox rash, acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15 or 20 mg/kg depending on the age group. Treatment with acyclovir reduced the maximum number of lesions (336 vs. greater than 500 lesions beyond 500 were not counted). Treatment with acyclovir also shortened the mean time to 50% healing (7.1 days vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with fever (temperature greater than 100°F) by the second day (19% vs. 57%). Treatment with acyclovir did not affect the antibody response to varicella-zoster virus measured one month and one year following the treatment.[33]

In two concurrent double-blind, placebo-controlled studies, a total of 883 normal patients, ages 2 to 18 years, were enrolled **within 24 hours** of the onset of a typical chickenpox rash, and acyclovir was administered at 20 mg/kg orally up to 800 mg 4 times daily for 5 days. In the larger study of 815 children ages 2 to 12 years, treatment with acyclovir reduced the median maximum number of lesions (277 vs. 386), reduced the median number of vesicular lesions by the second day of treatment (26 vs. 40), and reduced the proportion of patients with moderate to severe itching by the third day of treatment (15% vs. 34%).[35] In addition, in both studies (883 patients ages 2 to 18 years), treatment with acyclovir also decreased the proportion of patients with fever (temperature greater than 100°F), anorexia and lethargy by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36,37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at one month following treatment in patients receiving acyclovir compared to patients receiving placebo.[38]

Diagnosis

Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

CONTRAINDICATIONS

Acyclovir is contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS

Acyclovir tablets are intended for oral ingestion only.

PRECAUTIONS

General

Acyclovir has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**). The recommended dosage should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see **CLINICAL PHARMACOLOGY, Microbiology**).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients

Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections

Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Acyclovir tablets are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for six months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for one year in humans did not show any abnormalities in structure or number of chromosomes.[26]

Herpes Zoster Infections

Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox

Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that acyclovir treatment of chickenpox would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions

Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 5 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 5 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 580 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day, s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live

fetuses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the one-month study and were 24 to 48 times human levels in the six-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

Pregnancy

Teratogenic Effects: Pregnancy Category C

Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[42] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers

Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[43,44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS

Herpes Simplex

Short-Term Administration

The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration

The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%) and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%) and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%) and paresthesia (0.8%). Adverse events reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%) and headache (0.9%).

Herpes Zoster

The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%) and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%) and constipation (2.4%).

Chickenpox

The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%) and insomnia (0.4%).

Observed During Clinical Practice

Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General

Fever, headache, pain, peripheral edema, and rarely, anaphylaxis.

Nervous

Confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive

Diarrhea, elevated liver function tests, gastrointestinal distress, nausea.

Hemic and Lymphatic

Leukopenia, lymphadenopathy.

Musculoskeletal

Myalgia.

Skin

Alopecia, pruritus, rash, urticaria.

Special Senses

Visual abnormalities.

Urogenital

Elevated creatinine.

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6 hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

Treatment of Initial Genital Herpes

200 mg every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease

400 mg (one 400 mg tablet) 2 times daily for up to 12 months, followed by re-evaluation. See **INDICATIONS AND USAGE** and **PRECAUTIONS** for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy

200 mg every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster

800 mg (two 400 mg tablets, or one 800 mg tablet) every 4 hours orally, 5 times daily for 7 to 10 days.

Treatment of Chickenpox

Children (2 years of age and older)

20 mg/kg **per dose** orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg

800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients with Acute or Chronic Renal Impairment

Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>0 0-10	200 200	every 4 hours, 5x daily every 12 hours
400 mg every 12 hours	>10 0-10	400 200	every 12 hours every 12 hours
800 mg every 4 hours	>25 10-25 0-10	800 800 800	every 4 hours, 5x daily every 8 hours every 12 hours

Hemodialysis

For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a six-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

Peritoneal Dialysis

No supplemental dose appears to be necessary after adjustment of the dosing interval.[47,48]

HOW SUPPLIED

Acyclovir Tablets are available as white, unscored, round, flat-faced, beveled-edged tablets debossed "4267", on one side and "400" on the other side containing 400 mg acyclovir packaged in bottles of 100, 500 and 1000 tablets.

Acyclovir Tablets are available as white, unscored, oval-shaped tablets debossed "4268", on one side and "800" on the other side containing 800 mg acyclovir packaged in bottles of 100 and 500 tablets.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

PROTECT FROM MOISTURE.

Store between 15° and 25°C (59° and 77°F).

CAUTION: Federal law prohibits dispensing without prescription.

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MANUFACTURED BY
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0172
1/97
TD2

ACYCLOVIR TABLETS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074836

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 74-836 DRUG PRODUCT: Acyclovir DOSAGE FORM: Tablets

FIRM: Zenith Goldline Pharmaceuticals STRENGTHS: 400 mg & 800 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable on 1/10/097.

BIO STUDY: The single-dose bioequivalence study on 800 mg tablet (Lot #ND-249) was found acceptable, waiver for bioequavilance study for 400 mg tablet granted and dissolution testing on 800 mg tablet (Lot #ND-249) and 400 mg tablet (Lot #ND-248 acceptable by Amrat Patel on 8/5/96. Dissolution specifications for acyclovir product (tablet and capsule) were communicated to the firm in Control Document # BIO 96-240.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Active Ingredient: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.
Finish Dosage Form: Satisfactory for regulatory purposes on 11/14/96 from Philadelphia District.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Protocol: Satisfactory
Exp.Date: 24 months - 40°C, 75% R.H., 3 months and R.T. (25°C - 30°C), 12 months, smallest and largest container/closure system, 1 lot each strength. Lot # ND 248 (400 mg) and Lot # ND 249 (800 mg).
Container/Closure systems are the same.

LABELING: Container: Satisfactory in FP.
Insert: Satisfactory in FP.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
of 400 mg Lot # ND-248) and
units of 800 mg Lot # ND-249), source of NDS acceptable

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
of 400 mg Lot # ND-248) and
units of 800 mg , Lot # ND-249).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
of 400 mg and of
800 mg process the same.

4/4/97

CHEMIST: Norman Gregory DATE: 4/8/97

SUPERVISOR: John Simmons, Ph.D. DATE: 4/8/97

4/16/97

1. CHEMISTRY REVIEW NO. 3

2. ANDA 74-836

3. NAME AND ADDRESS OF APPLICANT
Zenith Goldline Pharmaceuticals, Inc.
140 Legrand Avenue
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies , that to the best of it knowledge, U.S. Patent No. 4,199,574 will expire on April 22, 1997, a New Chemical Entity exclusivity period expired on March 29, 1992, an indication of acute treatment of varicella zoster virus expired on April 26, 1993 and the indication of varicella infections (chickenpox) expired on February 26, 1995. Furthermore, the product will not be made available for sale until the expiration of U.S. Patent No. 4,199,574 on April 22, 1997.

Innovator: Burroughs Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
- 1/9/96 - Original.
- 3/13/96 - Response to refuse to file.
- 4/26/96 - Bio. Amendment.
- 7/26/96 - O/NC, Bio. information.
- 11/18/96 - O/NC, Bio. Amendment.
- 11/21/96 - Response to 1st def. letter (chem. & labeling).
- 1/20/97 - Response to phone memo, labeling.
- 3/26/97 - Response to 30 day letter.

FDA:
- 3/6/96 - Refuse to file, need LoA for active DMF.
- 3/21/96 - Acknowledgment.
- 8/5/96 - Bio. review.
- 8/15/96 - Bio. letter, acceptable
- 8/29/96 - 1st def. letter (chem. & labeling).
- 9/27/96 - Phone memo, regarding labeling.
- 1/17/97 - Phone memo, regarding labeling.
- 2/28/97 - Tentative approval letter, 2nd review.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

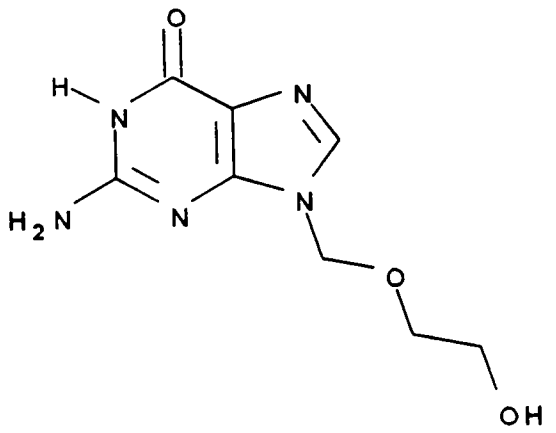
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCIES
400 mg & 800 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
$C_8H_{11}N_5O_3$; M.W. = 225.21



9-[(2-Hydroxyethoxy)methyl]guanine. CAS [59277-89-3]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
DMF, EER, Bio., labeling and method validation acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
4/8/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074836

BIOEQUIVALENCE REVIEW(S)

ANDA 74-836

Zenith Goldline Pharmaceuticals, Inc.
Attention: Karen Rocco
140 Legrand Avenue
Northvale NJ 07647

AUG 15 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Tablets 400 mg and 800 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of deaerated water at 37°C using USP 23 apparatus 2 (paddle) at 50 RPM. The test drug should meet the following specifications:

   Not less thar of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

9N

ANDA/AADA # 74-836 SPONSOR : Zenith Pharmaceuticals.
DRUG & DOSAGE FORM : Acyclovir 400 & 800 mg Tablets.
STRENGTH (s) : 800mg biostudy 400 mg waiver.
TYPE OF STUDY: (SBE) (SDF) MULT OTHER NOT fasted effects
STUDY SITE: CLINICAL :
ANALYTICAL :
STUDY SUMMARY : 800mg Single dose, 2-period, 2-treatment, 2-sequence crossover - Paired
800 mg Randomized, Single-dose, 2-way crossover under non-fasting condition - Paired Food effect on

Parameter	test	ref	ratio	90% CI (log).	
Cmax(ng/ml)(LSmean)	6.77	6.76	1.0	90.8 ; 113	Fast
	7.13	7.10	1.0		Fed
AUC(0-T) ngxhr/ml	8.30	8.27	1.0	90.5; 115	Fast
(LS mean)	8.74	8.80	1.0		Fed
AUC(0-Inf)ngxhr/ml	8.36	8.34	1.0	90.9 ; 114	Fast.
(LS mean)	8.80	8.79	1.0		Fed
Tmax hr	1.80	1.81	0.99		
Half-life hr	3.89	3.96	0.98		

DISSOLUTION : 800 mg Zenith Lot # NB-249 Ref. Lot # 401425
Conditions USP, Paddle, 50 RPM; 12 units; 900ml water

Time(min)	Test Mean(range)	Ref. Mean(range)
	800 mg 400 mg (Lot#NB-248)	800 mg 400 mg (Lot # 352193)
~~15~~ 10		
30		
45		
60		

Q = NLT dissolved @ in 30 minutes.

PRIMARY REVIEWER : A.P. Patel BRANCH : 3

INITIAL : _____ DATE : 8/5/96.

BRANCH CHIEF : Dr. R.M. Mhatre, Ph.D BRANCH : 3

INITIAL : _____ DATE : 8/5/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : _____ DATE : 8/5/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : N/A DATE : _____

DW

AUG 5 1996

Acyclovir Tablets
400 mg and 800 mg Tablets
ANDA #74-836
Reviewer: A.P.Patel
File: x:\apatel\74836SDW.196

Zenith Goldline Pharmaceuticals
Northvale, NJ
Submission Date:
Jan. 9, 1996
July 26, 1996
April 26, 1996

Review of Two BE Studies, Dissolution Data and a Waiver Request

Background:

Firm submitted a bio-study for review of acyclovir 800 mg and 400 mg tablets on Jan 9, 1996. An amendement was submitted for the requested (via Telcon) potency and content uniformity data on Zenith's acyclovir 400 mg tablets.

Objectives:

Review of Zenith's two *in vivo* bioequivalence studies comparing its 800 mg strength Acyclovir Tablets to Burroughs Wellcome's 800 mg strength, Zovirax® Tablets under fasting and non-fasting conditions. The firm submitted *in vitro* dissolution data for review.

Introduction:

Acyclovir is 9-[(2-hydroxyethoxy)methyl] guanine, a synthetic purine nucleoside analog with in vivo and in vitro inhibitory activity against (in decreasing order) herpes simplex types 1 and 2 viruses, varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Acyclovir is converted by enzymes present in virus-infected cells into an active form, acyclovir triphosphate, which interrupts viral DNA replication. Acyclovir capsules and suspension are indicated for treatment of initial episodes and management of recurrent herpes simplex virus genitalis in certain patients. The capsule, suspension, and tablet dosage forms are indicated for treatment of acute herpes zoster and chicken pox.

Acyclovir oral absorption is slow, variable, and incomplete. with absolute bioavailability estimated at about 15-30%. Peak blood concentrations occur approximately 1.5-2.5 hours following oral dosing. There are no active metabolites. Studies in which 0.5 to 15 mg/kg were administered I.V. to patients with normal renal function yielded elimination half-lives of 2 to 3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine.

Acyclovir is marketed as Zovirax® (Burroughs-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 mg and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 ml (NDA #19-909, 12/22/89).

Summary of Bioequivalence Study Procedures:

A. **BE Study under Fasting Conditions:**

1. Protocol and Study# B-09295

2. **Objective of the study:**

The objective of this study was to determine the bioequivalence of two acyclovir formulations after administration of single doses to healthy volunteers under fasting conditions.

3. **Study Design:**

A randomized, single-dose, two-period, two-treatment, two-sequence crossover

study (one week wash-out period) was conducted assessing the relative bioavailability of Zenith's Acyclovir 800 mg tablets vs. Wellcome's Zovirax® 800 mg tablets under fasting condition.

4. **Study sites:**
Clinical Facility: **Analytical Facility:**

Institutional Review Board Approval: Protocol approved by IRB

5. **Study dates:** Period 1 October 21, 1995
Period 2 October 28, 1995
Analytical study: 12/05/95 - 1/03/96 (includes repeat analysis)

6. **Drug Products:**
A. Test: 800 mg Acyclovir Tablets (Zenith, Lot #ND249, Exp. 9/3/96, batch size

B. Reference: 800 mg Zovirax® Tablets (Burroughs Wellcome, Lot #401425, Exp. 4/96, batch size - N/A)
All doses were administered with 240 ml of room temperature water following an overnight (10 hour) fast.

7. **Subjects:** The 48 subjects who entered in this study were normal healthy male volunteers with a mean age of 25.6 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations showing absence of any clinically significant findings. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

8. **Confinement:** During the confinement periods of this study, the subjects were housed and fed at the clinical facility.

9. **Food and fluid intake:** Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of tap water. Water was allowed ad lib. after 2 hours post-dose or soft drink without xanthines.

10. **Washout period:** 7 days

11. **Blood samples:** In each period, 10 mL of blood samples were collected in EDTA containing purple-top tubes at 0, 0.33, 0.67, 1, 1.33, 1.67, 2. 2.5, 3, 3.5, 4, 6, 8, 10,

12, 14 and 16 hours. Plasma was separated and all plasma samples were stored frozen at -20°C or below until analyzed.

12. **Subject safety monitoring:** Subjects were asked to spontaneously report any signs or symptoms that might be related to the drug products.

13. **Adverse reactions:** On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

14. **Analytical procedure:**

15. **Pharmacokinetics and statistical analysis:** Statistical analyses were performed on the pharmacokinetics parameters for acyclovir. The 90% confidence intervals were calculated for AUCt, AUCi and Cmax. PK parameters and drug plasma concentrations were evaluated statistically by ANOVA for differences due to treatments, study days, dosing sequence, and subjects within sequence.

B. BE Study under non-fasting Conditions:

1. Protocol and Study # B-01096

2. **Objective of the study:**
The objective of this study was to determine the bioequivalence of two acyclovir formulations after administration of single doses to healthy volunteers under non-fasting conditions.

3. **Study design:** Randomized, single-dose, two-way crossover study under non-fasting conditions.

4. **Study sites: As described under fasting study**
Institutional Review Board Approval: Protocol approved by IRB

5. **Study dates:** Period 1 February 4, 1996
Period 2 February 11, 1996
Period 3 February 18, 1996
Analytical study: 3/06/96 - 4/04/96 (includes repeat analysis)

6. **Drug Products:**
A. Test: 800 mg Acyclovir Tablets (Zenith, Lot #ND249, Exp. 9/3/96, batch size

B. Test: 800 mg Acyclovir Tablets (Zenith, Lot #ND249, Exp. 9/3/96, batch size dosed following high-fat breakfast.

C. Reference: 800 mg Zovirax® Tablets (Burroughs Wellcome, Lot #401425, Exp. 4/96, batch size - N/A) dosed following high-fat breakfast. All doses were

administered following over-night fast with 240 ml of room temperature water.

7. **Subjects:** Eighteen subjects who entered the clinical study were normal healthy male volunteers with a mean age of 25.8 years. and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations showing absence of any clinically significant findings. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

8. Details of the following categories is described under the fasting study and is not different in the non-fasting study: Confinement, Food and fluid intake, Blood samples, Subject safety monitoring, adverse reactions, Analytical procedure, Pharmacokinetics and statistical analysis.

III. **Validation of Assay Method for Plasma Samples:**

IV. ***In Vivo* BE Study Results with Statistical Analysis:**

A. **Study under fasting conditions:**

A total of 48 subjects participated in the study and 45 subjects completed two periods of clinical study successfully. Three subjects dropped out (#13, #22, and #37) for reasons not related to the study and their data were not included in the analysis.

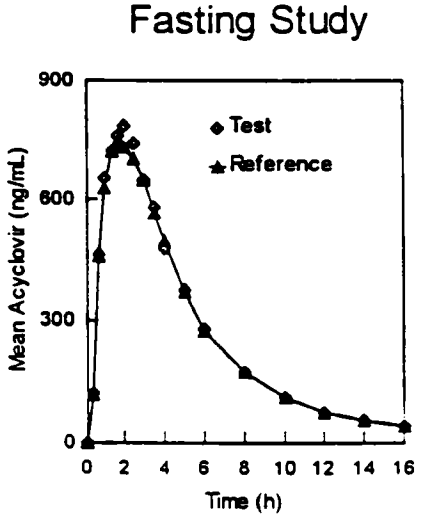
Adverse reactions: were followed according to the protocol of the study. No clinically significant adverse reactions were reported except three subjects (Subjects #13, 21, and 22) while on reference product, showed non-drug related, nausea and stomach cramps; and possibly drug related headaches. No treatment was required except for stomach cramps, 2x262 mg Dio-Tame was given.
No clinically significant adverse reactions were reported under the non-fasting conditions.

1. **Mean plasma levels**

The mean plasma levels for the test and reference products are comparable as shown in Table 8. The test/reference ratios for the mean plasma levels range from 0.96 to 1.07. ANOVA did not detect a difference in mean plasma concentrations at any plasma collection time point.

Table 8: Mean plasma acyclovir levels (ng/mL) for test and reference products.

Time	Test (T)	Reference (R)	Ratio
hour	Mean	Mean	T/R
0.00	0.00	0.00	-
0.33	123.57	121.23	1.02
0.67	467.03	463.09	1.01
1.00	654.22	631.87	1.04
1.33	723.80	721.13	1.00
1.67	759.49	746.51	1.02
2.00	785.53	733.93	1.07
2.50	743.27	704.58	1.05
3.00	649.00	651.42	1.00
3.50	583.69	570.00	1.02
4.00	482.18	501.33	0.96
5.00	377.49	376.26	1.00
6.00	281.70	276.42	1.02
8.00	175.14	178.29	0.98
10.00	112.05	111.94	1.00
12.00	77.50	76.93	1.01
14.00	55.08	54.95	1.00
16.00	43.18	43.39	1.00



2. **Summary of Pharmacokinetics Data:** Described in tables 9 and 10.

Table 9. **Non-transformed Data**

Parameter (LSMean)	**Test** (1x800mg)	**Ref** (1x800mg)	**Ratio of means** (Test/Ref.)	**% Difference** 100*(T-R)/R
AUC_{0-t}	4274.21	4211.91	1.01	1.5
$AUC_{0-\infty}$	4528.52	4466.11	1.01	1.4
Cmax	923.08	921.09	1.00	0.22
Tmax	1.80	1.81	0.99	0.55

Table 10. **90% C.I.Limits of Ln-transformed parameters:**

	AUC_{0-t}	$AUC_{0-\infty}$	Cmax
Test (LSMean)	8.30	8.36	6.77
Ref (LSMean)	8.27	8.34	6.76
Ratio: Test/Ref	1.00	1.00	1.00
90% C.I.	90.5; 115	90.9; 114	90.8; 113

The 90% C.I. are within the Agency's bioequivalence requirements, between 80% - 125%, fasting study is acceptable. The ratio of test/reference for pharmacokinetics parameters are not different from beach other.

3. Differences between test (mean) and reference (mean) non-transformed pharmacokinetics parameters:
The test (LSMEAN) values differ from the corresponding reference (LSMEAN) values by 1.5% for AUC_{0-t}, 1.4% for $AUC_{0-\infty}$, less than 1% for C_{max}, and less than 1% for T_{max}. There were no significant effects of differences in PK parameters due to dosing periods or sequence.

B. **Study under non-fasting Conditions:**

A total of 18 subjects participated in the study and 17 subjects completed three periods of the study successfully. There was one drop-out, subject #2 after period one, due to an automobile accident unrelated to the study and there was no missing sample. Data from subject #2 are not included for analysis.

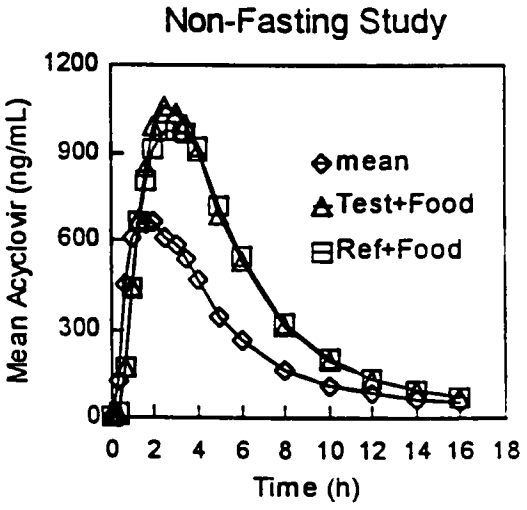
1. **Mean plasma levels**

Table 12 shows the plasma acyclovir-time data for the food study. The plasma levels after dosing were higher in fasting subjects initially up to 1h, there after the plasma levels under non-fasting conditions were much higher than those under fasting conditions. The plasma levels under non-fasting conditions were comparable between the test and reference products.

Table 11. Mean plasma acyclovir levels for test and reference products

Time hour	T_Fast mean	T+Food mean	R+Food mean	Ratio T+F /R+F
0.00	0.00	0.00	0.00	0.00
0.30	128.20	10.80	11.10	0.97
0.70	456.50	170.10	168.60	1.01
1.00	610.20	446.40	435.20	1.03
1.30	656.50	674.90	665.10	1.01
1.70	659.90	853.60	805.50	1.06
2.00	662.10	995.20	911.60	1.09
2.50	608.80	1065.00	977.50	1.09
3.00	584.20	1043.00	974.50	1.07
3.50	539.00	999.80	970.20	1.03
4.00	472.20	906.70	919.90	0.99
5.00	345.10	687.50	722.00	0.95
6.00	265.10	528.80	544.80	0.97
8.00	163.50	311.40	319.70	0.97
10.00	109.10	193.30	199.20	0.97
12.00	83.80	131.40	133.20	0.99
14.00	63.80	95.20	91.10	1.05
16.00	52.20	70.40	68.40	1.03

T=Test; R=Reference; T+F= Test+Food; R+F=Reference+Food



2. **Pharmacokinetics parameters**

The test/reference ratios for the PK parameters under non-fasting conditions are shown in Table 12.

Table 12. **Ln-Transformed Pharmacokinetics Data (LSMeans)**

	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
Test-Fast	8.19	8.31	6.56
Test+ food (T+F)	8.74	8.80	7.13
Reference+ food (R+F)	8.73	8.79	7.10
(T+F)/(R+F)	1.00	1.00	1.00
(T+F)/(Test-Fast)	1.07	1.06	1.09

The ratios for the test/reference ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and Cmax are near unity. The differences in ratios meet the Agency's requirements (±20%) for the test product. Non-fasting study is acceptable. The differences in pharmacokinetics parameters of products were not significantly different, α=0.05, when dosed with food. There were no significant effects of differences in PK parameters due to dosing periods or sequence except for Cmax values in periods I and II and in Kelm value between sequence groups (most likely due to small sample size (3) for each group.

Effect of Food on acyclovir absorption:

The plasma acyclovir levels were different for the test product when dosed with and without food as in the table 12. The total absorption AUC_{0-t} and $AUC_{0-\infty}$ was increased (statistically significant) by about 61% and 54%, respectively; and C_{max} and T_{max} was increased (statistically significant) by 62% and 70%, respectively.

V. **Waiver for 400 mg Strength tablet:**

Proportional formulation between test 800 mg tablet and test 400 mg tablets is shown in Table 13. Comparative dissolution data between test 400 mg and reference 400 mg tablets are acceptable(table 20). Waiver from bio-study for test 400 mg tablets may be granted.

VI. **Formulation**

Table 13. shows the composition of the test products. 400 mg and 800 mg Acyclovir Tablets by Zenith. The 400 mg and 800 mg strengths are exactly proportional in active and inactive ingredients.

The reference product contains FD&C Blue No.2. magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Table 13. Composition of Zenith's Acyclovir Tablets

Ingredient	400 mg tablet, mg	800 mg tablet, mg	Ratio: 400/800
Acyclovir, USP	400.0	800.0	0.5
Povidone, USP			
Microcrystalline cellulose, NF			
Sodium starch glycolate, NF			
Starch, NF			
Magnesium stearate, NF			
Total tablet weight	530	1060	0.5

VII. In Vitro Testing

1. Potency and content uniformity

Assay and content uniformity data are summarized for the test and reference, 800 mg products in Table 14 and are acceptable. The batch size of the test product was ablets. Potency and content uniformity data for the test 400 mg tablets are not provided.

Table 14. Potency and Content Uniformity

Product	Lot No.	Potency, %	% Content uniformity (%CV)
Zovirax, 800 mg	401425	99.1	98.4 (2.0)
Test, 800 mg	ND-249	99.0	99.5 (1.2)
Test, 400 mg	ND-248	100.0	99.6 (0.8)

2. Dissolution testing data

The dissolution testing was performed in 900 mL of deionized water using apparatus 2 (paddle) at 50 RPM with dissolution specifications of NLT dissolved in 60 minutes. The FDA method calls for "Q" NLT dissolved in 30 minutes. The test and reference 400 mg and 800 mg products dissolution data (table 15) are acceptable.

Table 15. In Vitro Dissolution Testing

Drug: Acyclovir
Dose Strength: 800 mg and 400 mg tablets
ANDA No.: 74-836
Firm: Zenith
Submission Date: Jan 9, 1996

I. **Conditions for Dissolution Testing:**

Paddle RPM: 50
No. Units Tested: 12
Medium: Water: Volume: 900 mL
Specifications: NLT Q) of the labeled amount is dissolved in 60 minutes.
Reference Drug: Zovirax 800 mg and 400 mg tablets of Burrougns Wellcome
Assay Methodology:

II. **Results of In Vitro Dissolution Testing:** 800 mg tablets - bio-study requirement

Sampling Times (Minutes)	Test Product Lot # ND-249 Strength 800 mg tablets			Reference Product Lot # 401425 Strength 800 mg tablets		
	Mean %	Range	%CV	Mean %	Range	%CV
10	53.6		8.0	86.2		3.1
20	85.6		3.4	93.1		2.6
30	93.6		2.8	96.3		3.2
45	97.6		2.1	98.1		3.3
60	98.3		1.5	99.7		3.1

III. **Results of In Vitro Dissolution Testing:** 400 mg tablets - waiver requirement

Sampling Times	Test Product Lot # ND-248 Strength 400 mg tablets			Reference Product Lot # 352193 Strength 400 mg tablets		
Minutes	Mean %	Range	%CV	Mean %	Range	%CV
10	82.0		5.7	85.2		6.5
20	90.3		2.3	91.9		3.3
30	92.2		1.9	94.9		2.7
45	95.0		2.0	97.1		2.2
60	96.3		1.5	98.6		2.2

VIII. Comments

1. Study under fasting conditions:

A total of 45 subjects participated in the study and completed two periods of study successfully. Three subjects didn't complete the clinical study for reasons not related to the study and their data were not included in the analysis. There was no missing sample. The mean plasma levels for the test and reference products are comparable. The test/reference ratios for the non-transformed and ln-transformed PK parameters range 1.0 to 1.01. The 90% confidence intervals for the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and Cmax were all within the 80-125% range.

2. **Study under non-fasting Conditions:**

A total of 17 subjects completed three periods of the study successfully. There was one drop-out not related to the study. There was no missing sample. The plasma acyclovir-time data for the food study showed a significant food effect on the absorption of acyclovir. The plasma levels under non-fasting conditions were much higher than those under fasting conditions. The plasma levels under non-fasting conditions were comparable between the test and reference products. The test/reference ratios for ln-transformed AUCt, AUCi and Cmax are near unity and meet the Agency's requirements.

3. **Waiver of bio-study for 400 mg Strength:**

Waiver from *in vivo* bioequivalence requirements is approveable. The dissolution testing conducted by Zenith Goldline Pharmaceuticals, on its Acyclovir 400 mg tablets (Lot#ND-248), is acceptable. The formulation for the 400 mg strength is proportionally similar to the 800 mg strength of the test product which underwent acceptable bioequivalence testing.

4. **Assay validation:**

Pre-study validation and within-study validation are acceptable.

5. **Adverse reaction:**

Under fasting conditions no clinically significant adverse reactions were reported. No treatment was required except for stomach cramps, 2x262 mg Dio-Tame was given. All incidences occurred while on reference product. No clinically significant adverse reactions were reported under the non-fasting conditions.

6. The batch size of the 800 mg test product was tablets.

7. The formulations of the 400 mg and 800 mg test products are proportional in active and inactive ingredients.

8. **Dissolution testing:**

Firm has set "Q" NLT dissolved in 60 minutes. In FDA method, "Q" is set at NLT in 30 minutes. The data meets the requirement.

IX. **Deficiency:** None

X. **Recommendation**

1. The single-dose bioequivalence study #B-09295 and B-01096 conducted by Zenith Goldline Pharmaceuticals, on its Acyclovir 800 mg Tablets, lot #ND-249 comparing it to Zovrax® 800 mg Tablets, lot #401425, manufactured by Burroughs Wellcome, is found to be acceptable by the Division of Bioequivalence. The study demonstrates that Zenith's Acyclovir Tablet, 800 mg is deemed bioequivalent to the

reference product, Zovrax[R] Tablets, 800 mg, manufactured by Burroughs Wellcome.

2. The dissolution testing conducted by Zenith Goldline Pharmaceuticals, on its Acyclovir 800 mg tablets (Lot #ND-249) and 400 mg tablets (Lot#ND-248), is acceptable. The formulation for the 400 mg strength is proportionally similar to the 800 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* bioequivalence study requirements for the 400 mg tablet of the test product is granted. The Division of Bioequivalence deems Acyclovir Tablet, 400 mg, manufactured by Zenith Goldline Pharmaceuticals to be bioequivalent to Zovrax[R] Tablet, 400 mg, manufactured by Burroughs Wellcome.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deaerated water at 37°C using USP 23 apparatus 2 (paddle) at 50 RPM. The test drug should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approveable.

The firm should be informed of the recommendations.

8/2/96

A.P.Patel
Division of Bioequivalence
Review Branch III

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FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D.
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Division of Bioequivalence

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Concur:
Kieth Chan, Ph.D.
Director
Division of Bioequivalence

Date: 8/5/96

cc: ANDA #74-836 (original. duplicate), HFD-600 (Hare), HFD-630, HFD-344 (C.Viswanathan), HFD-658 (R.M.Mhatre, A.P.Patel), Drug File, Division File.